

# Plasma Cell Dyscrasias & The Kidney

How they affect the kidney?

When to suspect? How to diagnose?

**Mohammed Abdel Gawad**

Nephrology Specialist

Kidney & Urology Center (KUC) - Alexandria

[drkawad@gmail.com](mailto:drkawad@gmail.com)



Amyloidosis

Multiple  
Myeloma

Imunotactoid  
GN

Fibrillary  
GN

Dyscrasias

Gamma  
Globulin

Monoclonal  
vs  
Polyclonal

Light vs  
Heavy Chain

Gammopathy

SPE /  
Immunofixation

LCDD,  
HCDD



# Plasma Cell Dyscrasias



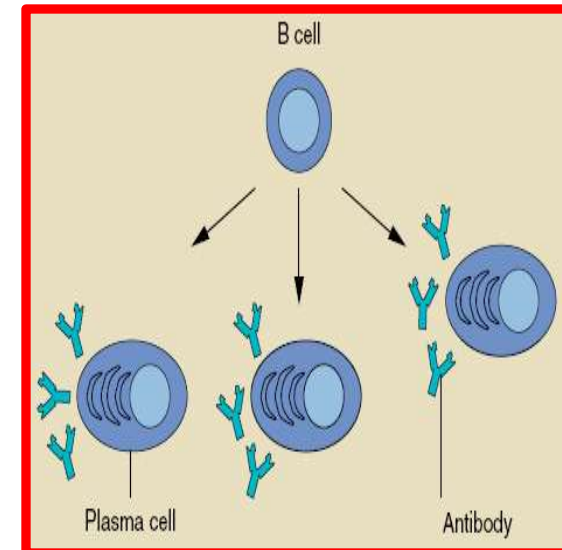
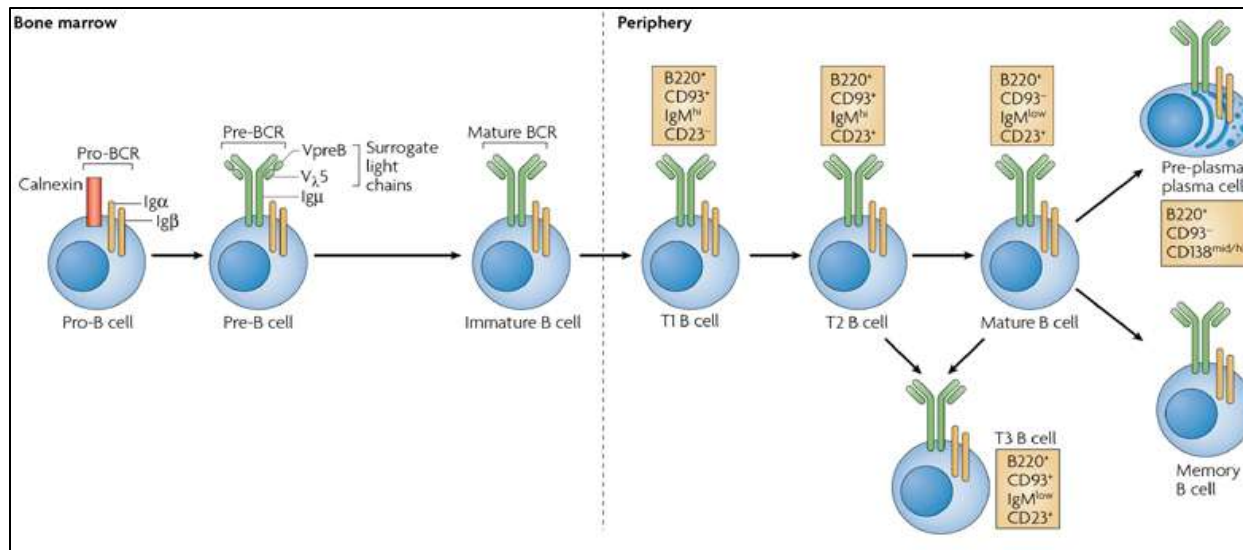
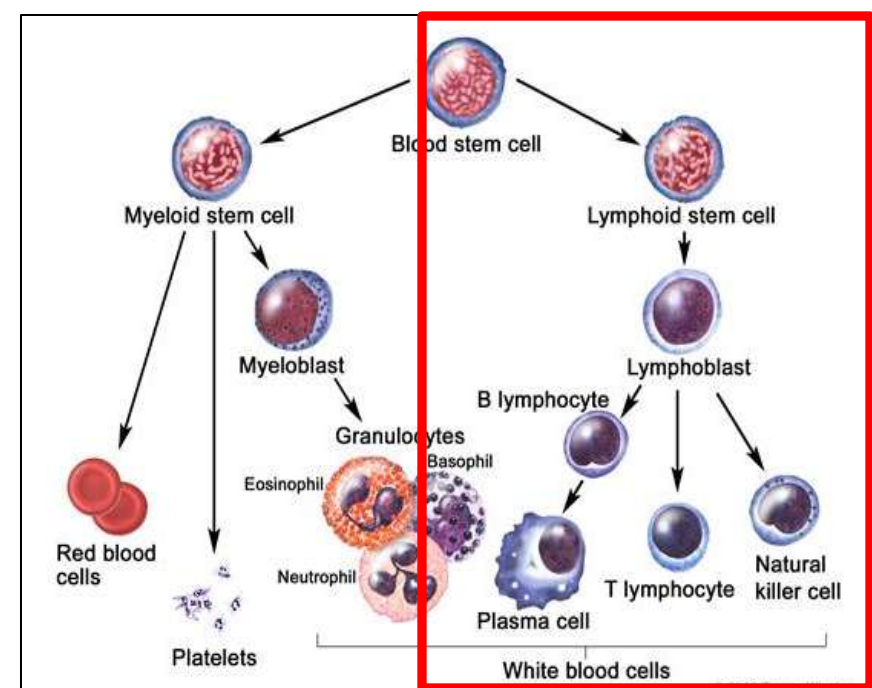
## Nephrology Perspectives

*How they affect the kidney?*

*When to suspect? How to diagnose?*

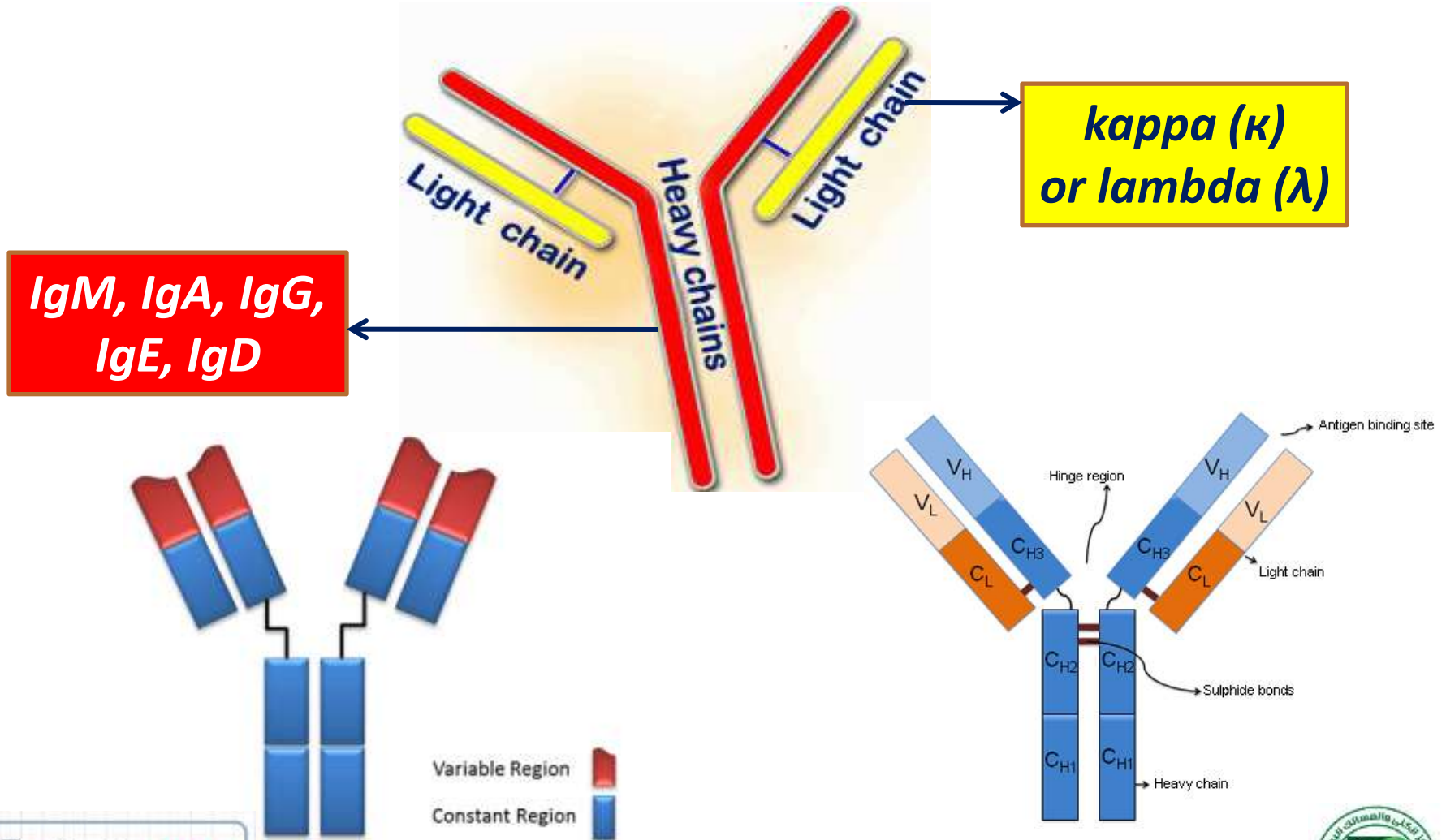
# Plasma Cells

- Plasma cells ultimately originate in the bone marrow; however, these cells leave the bone marrow as B cells, before terminal differentiation into plasma cells normally in lymph nodes.
- They are the primary mediators of humoral immunity, secreting antigen-specific immunoglobulins



# Immunoglobulin (Antibody, Gama Globulin) Structure

*(Some Igs are not gamma globulins, and some gamma globulins are not Igs)*

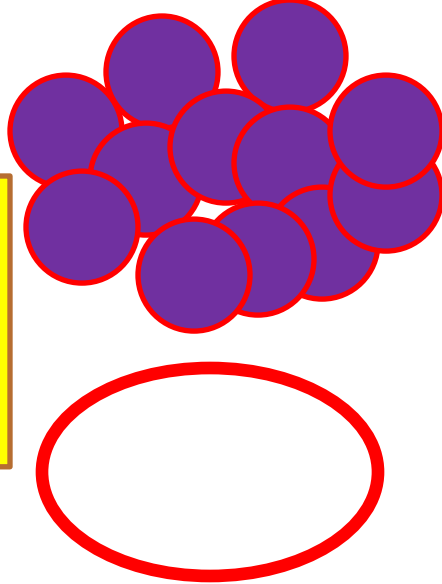


# Monoclonal Abs (Ig, Gama Globulin)

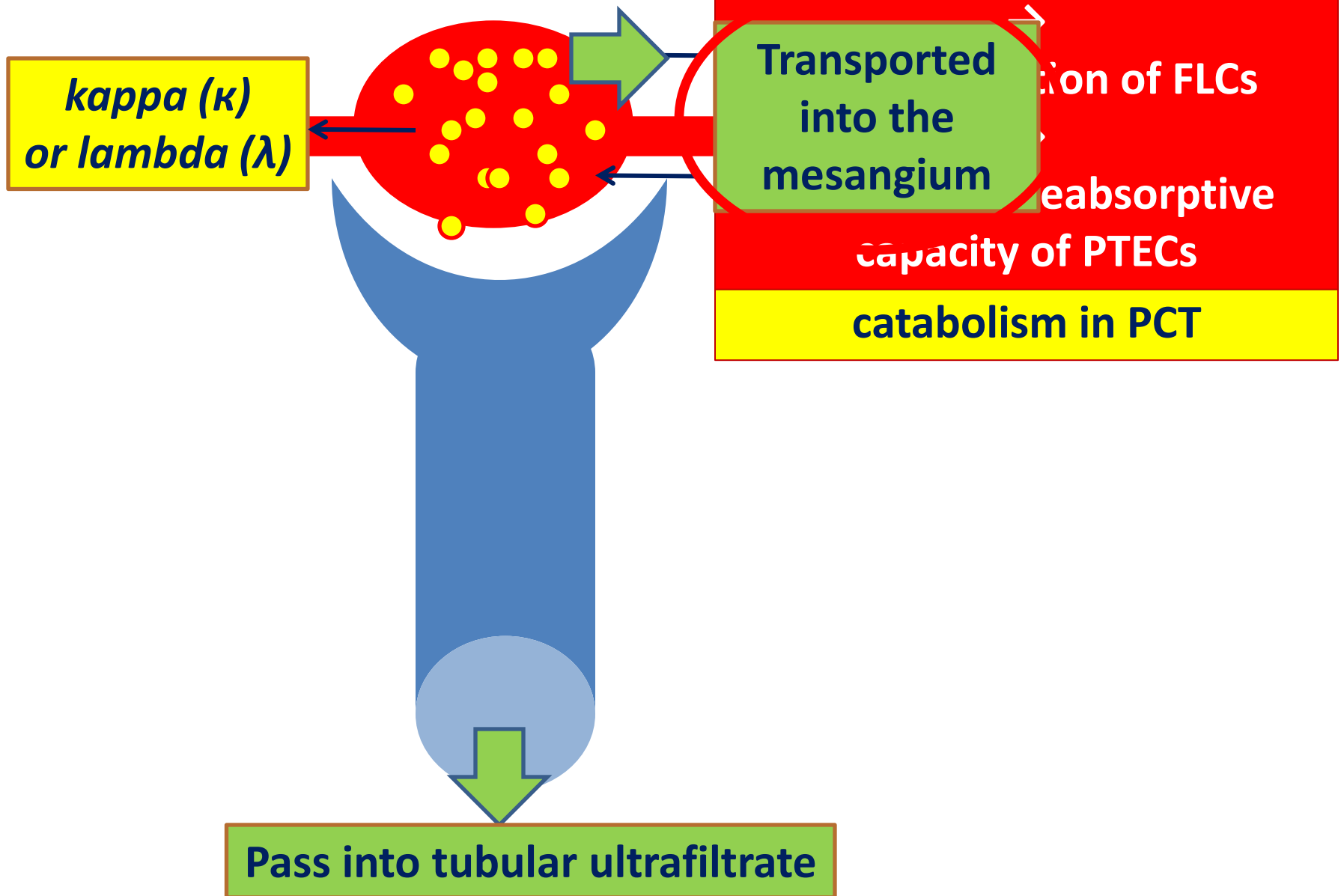
## Polyclonal Abs (Ig, Gama Globulin)

- Fairfax KA, Kallies A, Nutt SL, et al. Semin Immunol. 2008;20:49
- Radbruch A, Muehlinghaus G, Luger EO, et al. Nat Rev Immunol. 2006;6:741-750.

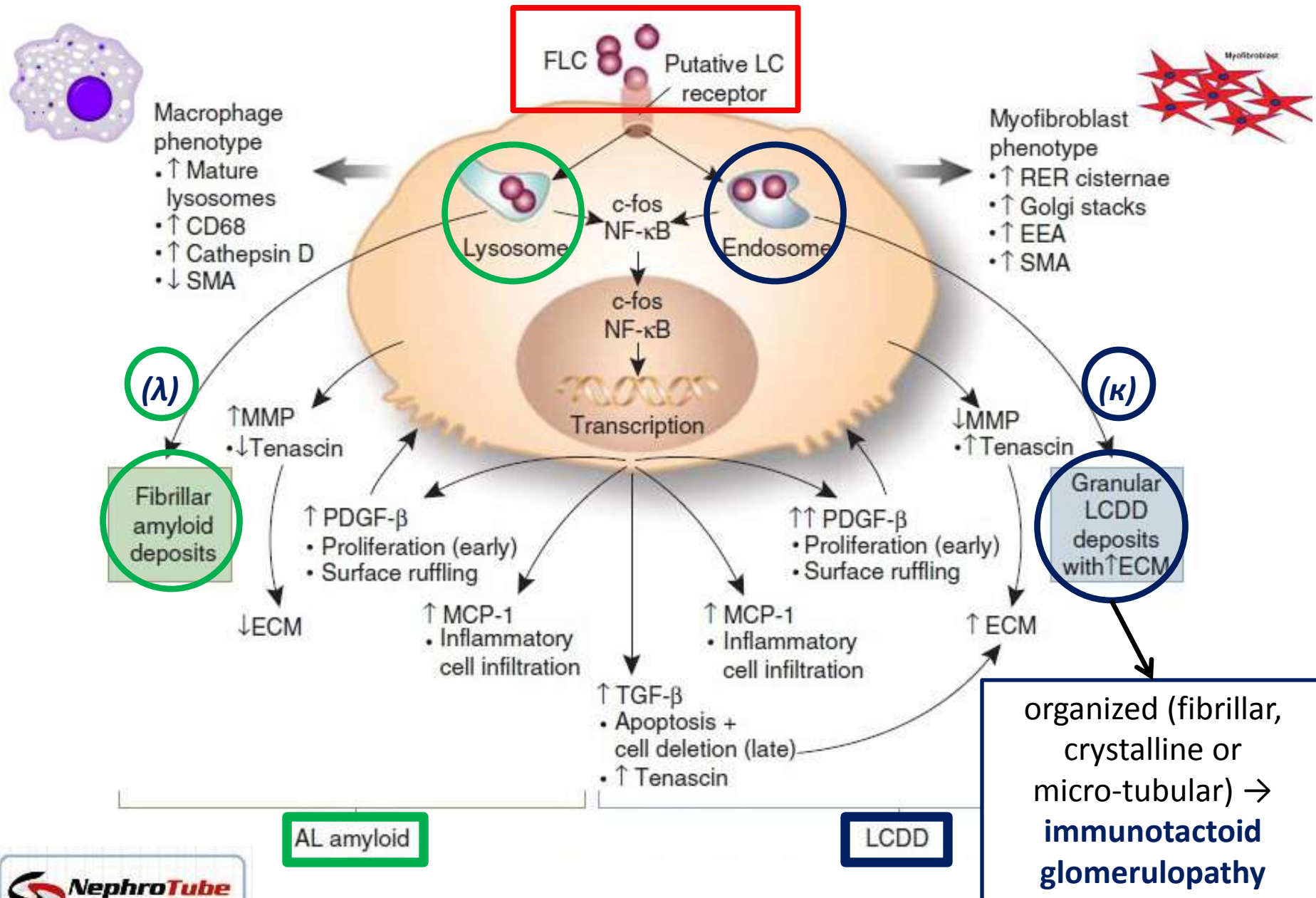
***How they  
affect the  
kidney?***



**Plasma Cell Dyscrasias**  
(Clonal proliferation of plasma cells)



Interactions of FLCs with mesangial cells (MCs): AL amyloidosis (left) and light chain deposition disease (LCDD; right).



# Primary (AL) Amyloidosis

FLC  $\lambda$



Serum amyloid protein (SAP)

Protects fibrils from proteolytic degradation

Glycosaminoglycans (Heparan sulfate)

Fibrillary, misfolded, nonbranching,  $\beta$ -pleated sheet structures (7-12nm)

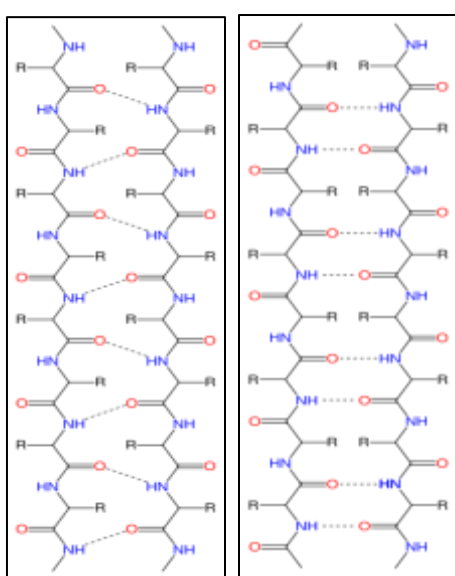
Fibrillar amyloid deposits

AL amyloid

major site in glomeruli, with arterioles, arteries, interstitium, and tubular basement membranes involved to lesser degrees.

Antiparallel  $\beta$ -Sheets

Parallel  $\beta$ -Sheets



Herrera GA, et al. Ultrastruct Pathol 1999; 23: 107–126.  
Herrera GA. Ann Diagn Pathol 2000; 4: 174–200.  
Tennent GA et al. Proc Natl Acad Sci USA 1995; 92: 4299–4303.  
Scholefield Z et al. J Cell Biol 2003; 163: 97–107.  
Yamaguchi I et al Kidney Int 2003; 64: 1080–1088.



# Primary (AL) Amyloidosis

FLC 8  
(λ)

# Secondary (AA) Amyloidosis

Fibrils are composed of the serum Amyloid A protein.

## Causes of AA

Rheumatoid arthritis

Other arthropathies: Ankylosing  
spondylitis, psoriatic arthropathy

IBD

Chronic suppurative infections:  
bronchiectasis, osteomyelitis

TB, Leprosy

Malignancy (RCC, Lymphoma)

FMF

Cystatin C

Hereditary, AD

Fibrillar  
amyloid  
deposits

. amyloid

Novak L et al. Nephrol Dial Transplant 2004;19:3050.

Jaccard A. Moreau P, Leblond V, et al. N Engl J Med 2007; 357 (11): 1083–1093.

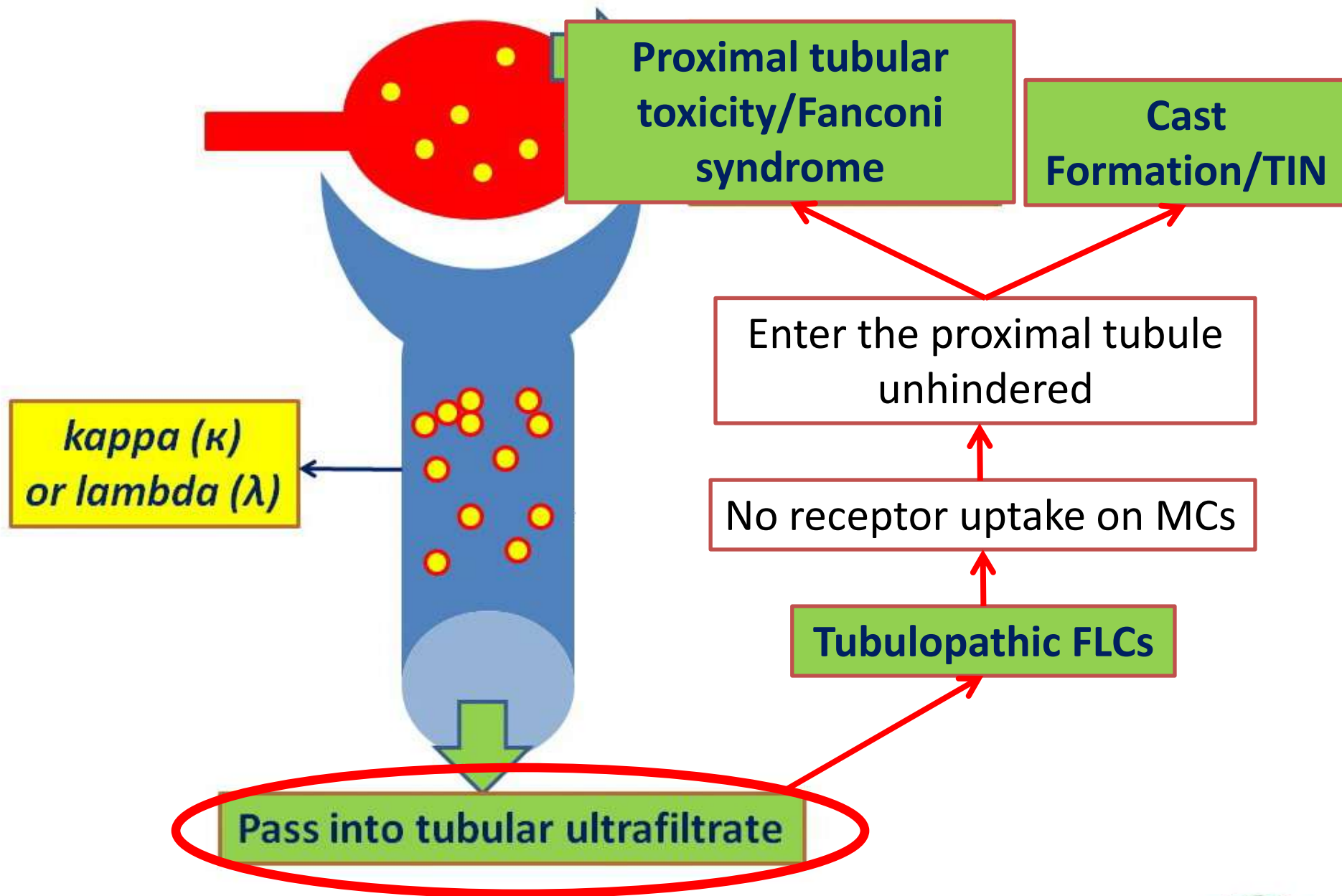
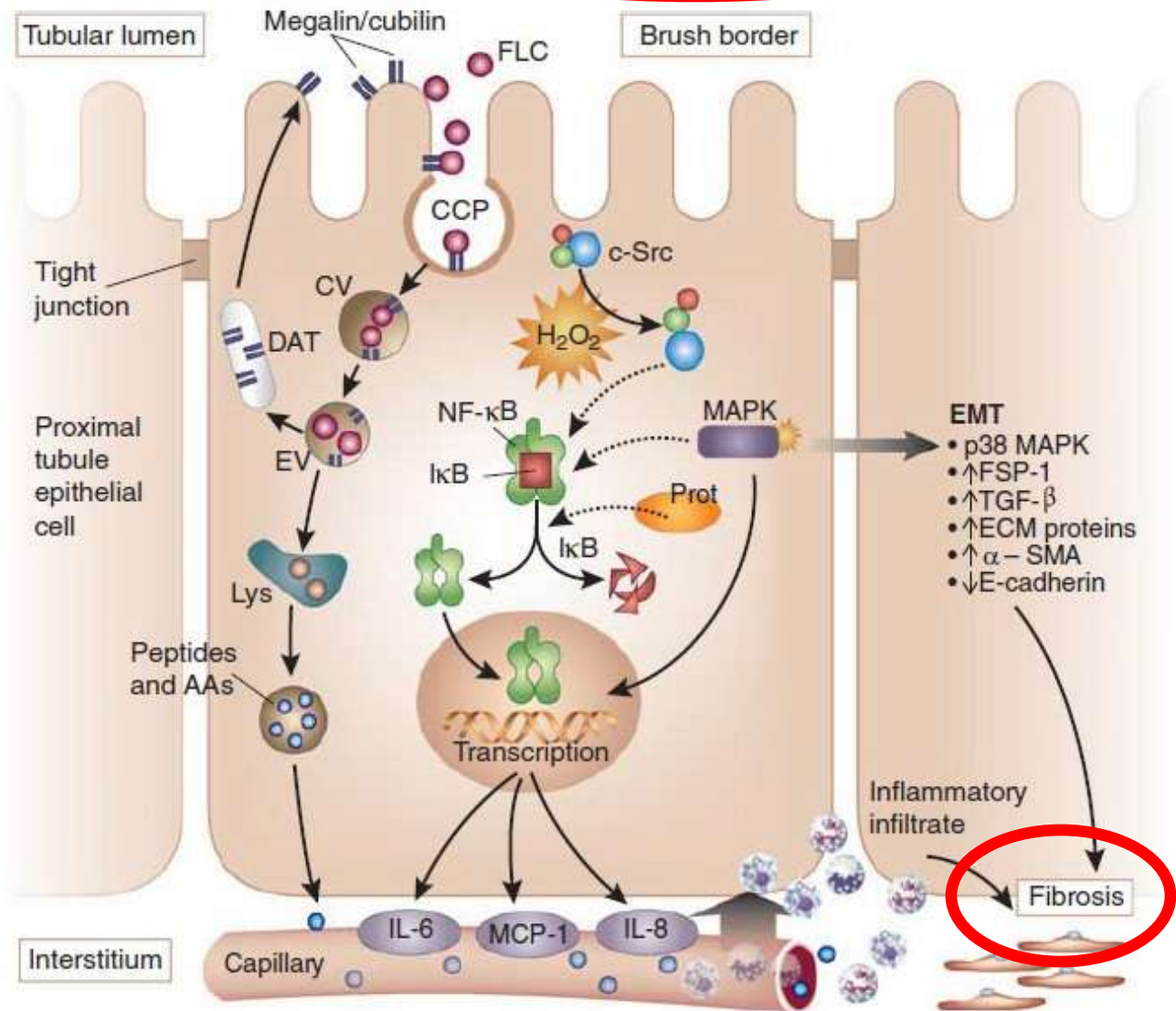
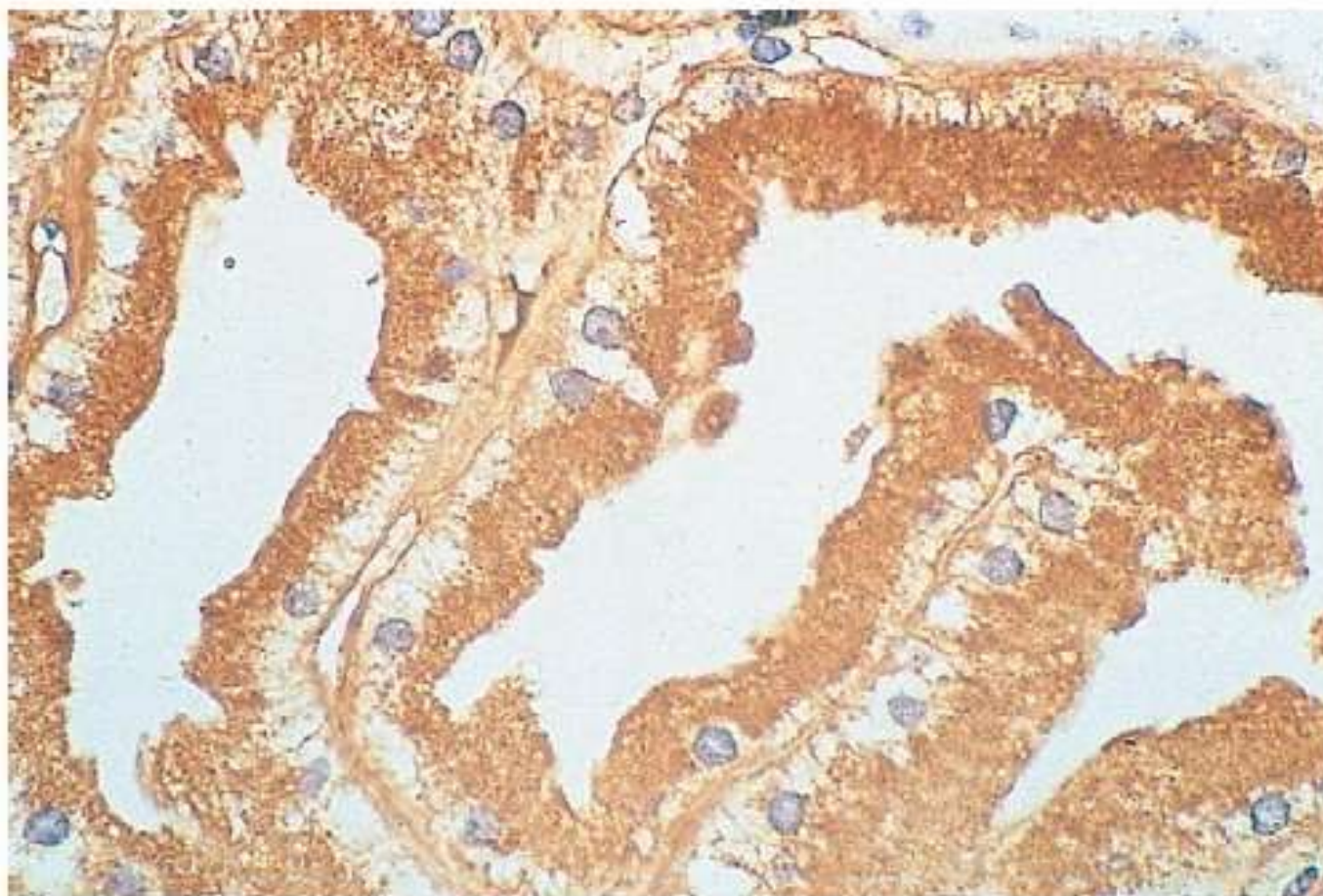


Figure 2 | Interactions of free light chains (FLCs) with proximal tubule epithelial cells (PTECs).

The classical histological finding is intralysosomal crystalline deposits of FLCs within PTECs





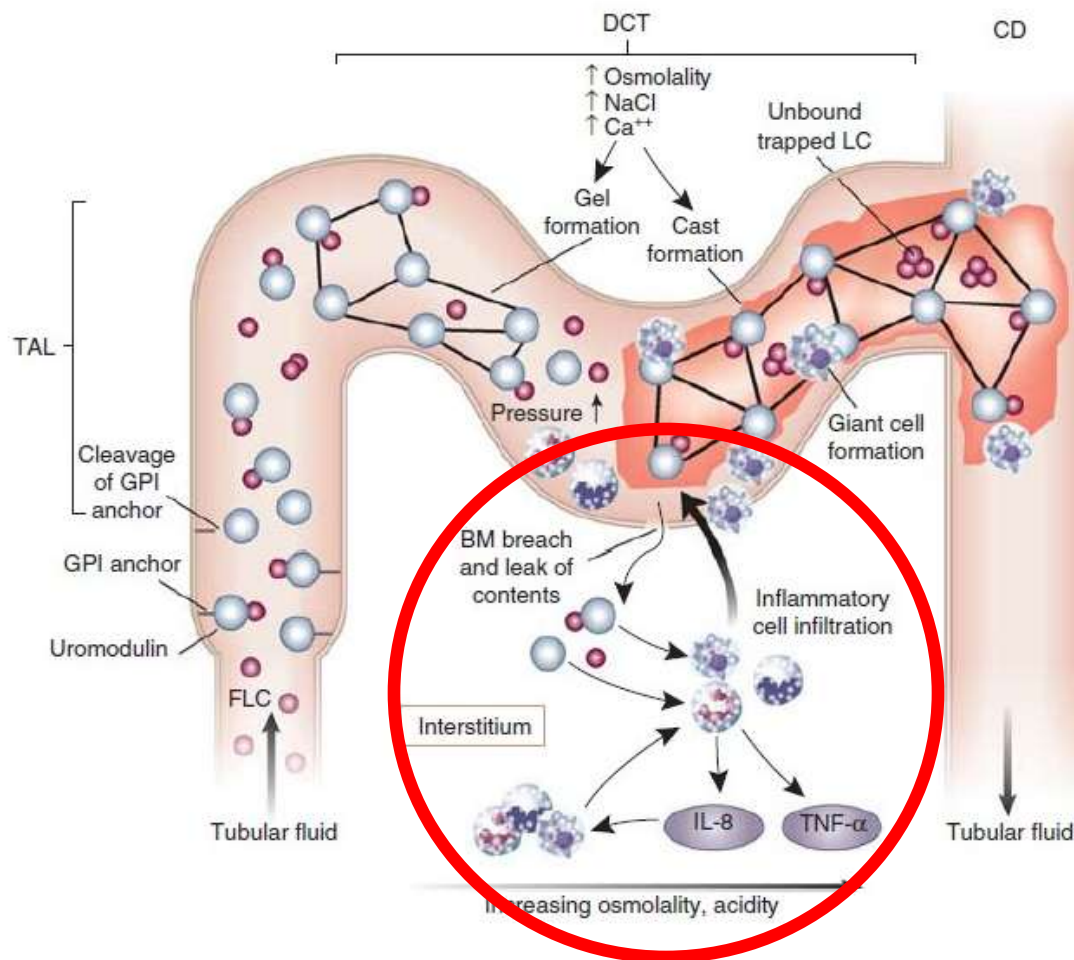
**Figure 63.2 Uptake of light chains by proximal tubular cells.** Renal biopsy specimen from a patient excreting  $\kappa$  light chains. Immunoperoxidase staining showing  $\kappa$  light chains along the brush border and in the cytoplasm of the PTC (brown stain).

Figure 3 | Light chain interactions in the distal nephron.

Fractured **DCT** protein precipitates (casts), consisting of **uromodulin & FLC**

Cast formation is **characteristic** for **Multiple Myeloma**. But it may also be seen in up to a **third of cases of LCDD**, but is **rare in AL amyloidosis**

Cast is characterized by **tubulointerstitial inflammation and fibrosis**



# When to suspect Amyloidosis clinically ?



## Nephrotic syndrome

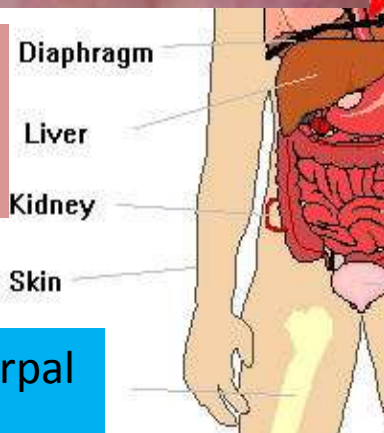
(severe edema, often with anasarca and pleural effusions)



**Figure 26.6** Macroglossia in a patient with AL amyloidosis. (Copyright 2012, Elsevier)



Hepatomegaly  
Easy bruising, Factor IX and  
X deficiency with bleeding



Peripheral neuropathy (carpal  
tunnel syndrome)

Involvement of the  
primary h

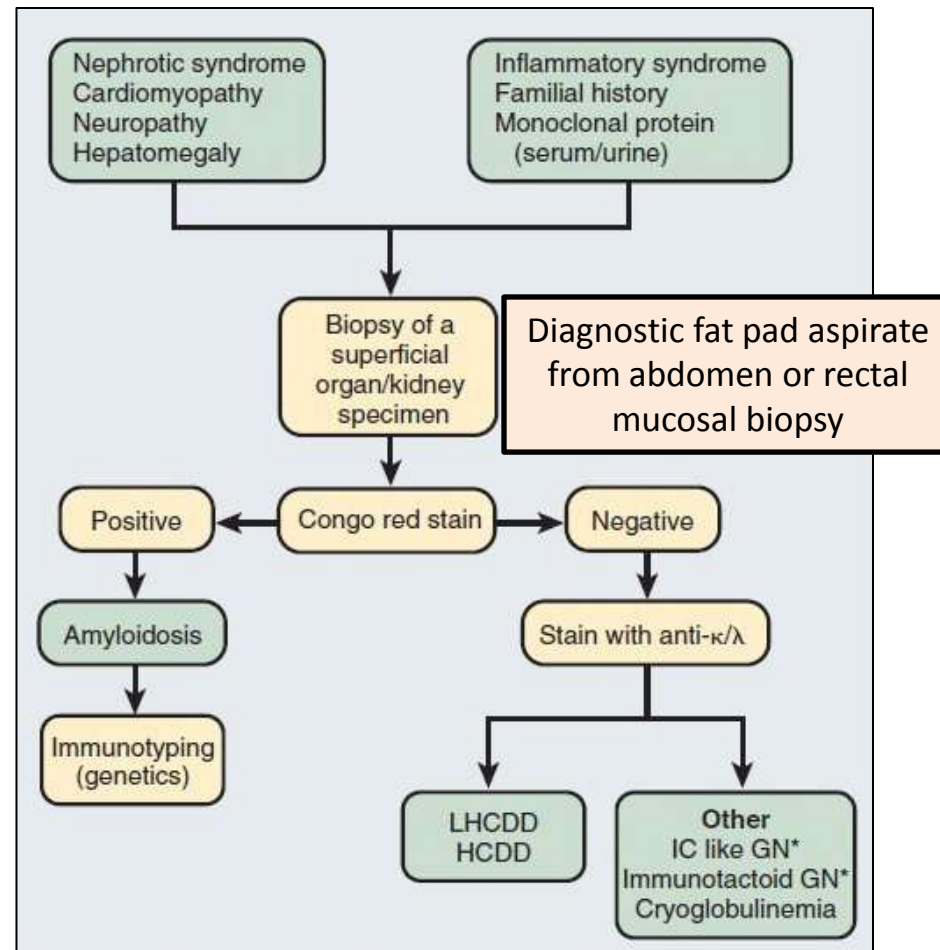


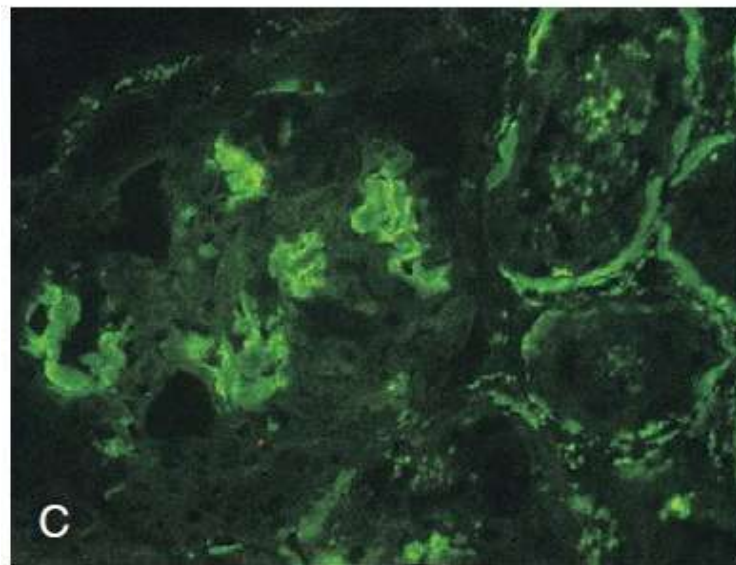
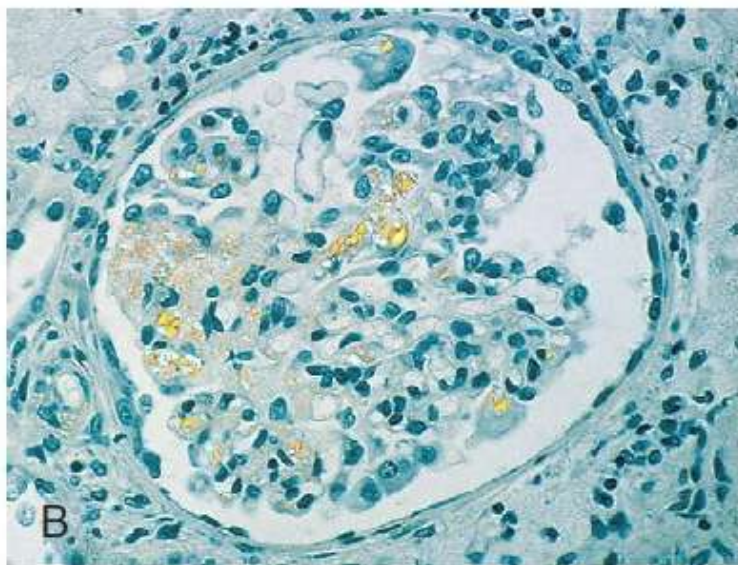
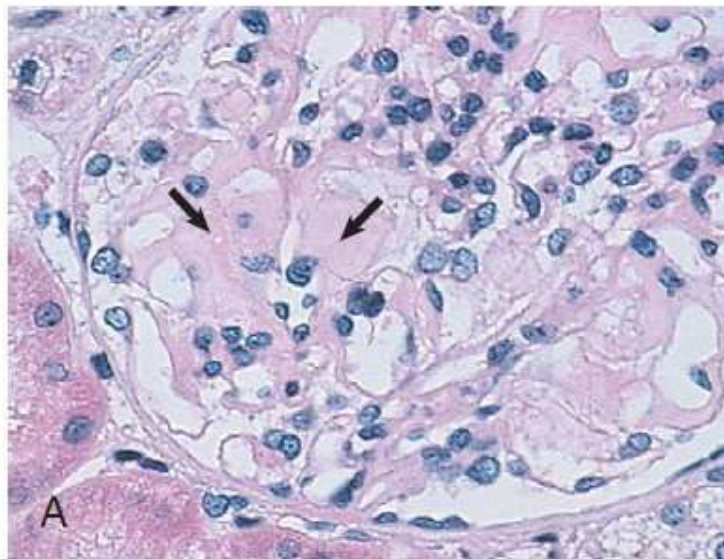
**Figure 26.7** Skin involvement in AL amyloidosis. Noninfiltrated purpuric macule of the superior eyebrow, very typical of AL amyloidosis. (Copyright 2012, Elsevier)

# When to suspect LCDD Clinically?

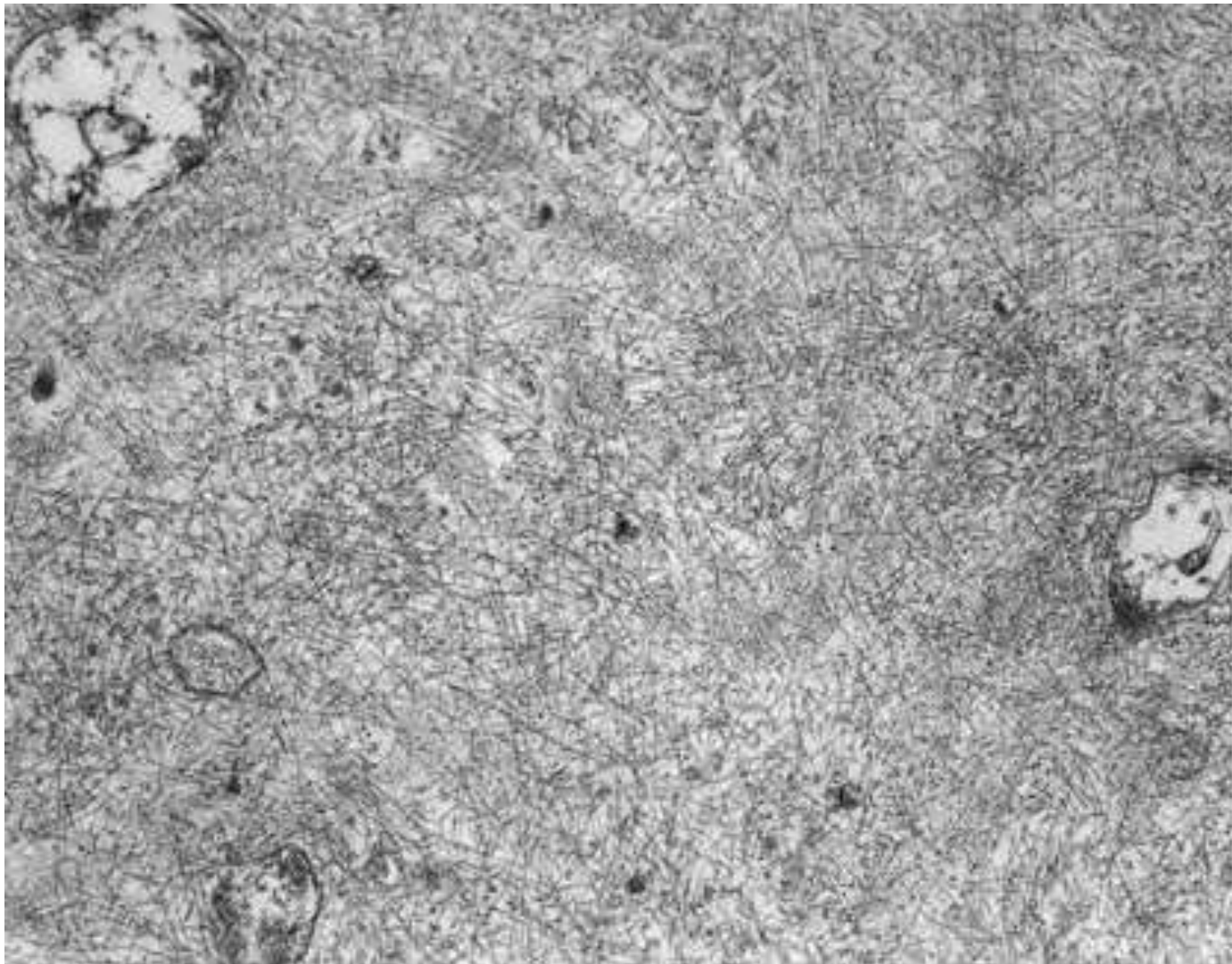
Characteristics	LCDD/LHCDD	HCDD
Male-to-female ratio	1.7	0.8
Age, yr (range)	57 (28–94)	57 (26–79)
Hypertension (%)	53	90
Renal failure (serum creatinine $\geq 130 \mu\text{mol/l}$ ) (1.47 mg/dl)	93	83
Nephrotic syndrome* (%)	36	46
Hematuria (%)	45	89

# Stepwise Approach - AL Amyloidosis or LCDD Diagnosis?





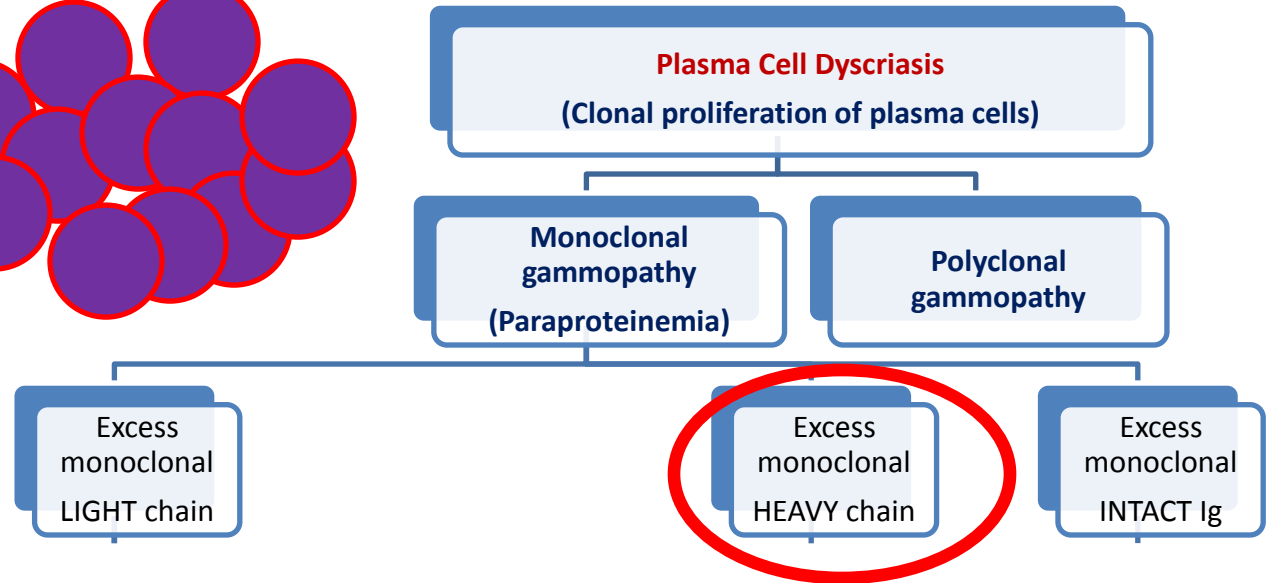
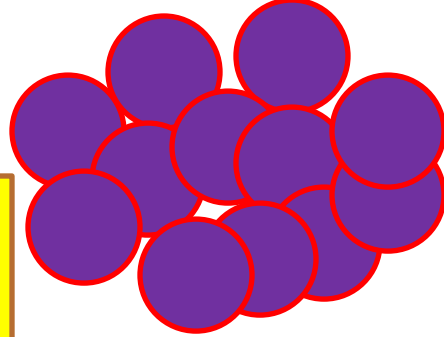
**Figure 26.3 Amyloidosis.** **A**, Amyloid deposits (*arrows*) in a glomerulus. (Hematoxylin-eosin; magnification  $\times 312$ .) **B**, Congo red staining. Apple-green birefringence under polarized light. (Magnification  $\times 312$ .) **C**, Immunofluorescence with anti- $\kappa$  antibody. Note glomerular and tubular deposits. (Magnification  $\times 312$ .) (Courtesy Dr. Béatrice Mougenot, Paris, France.)



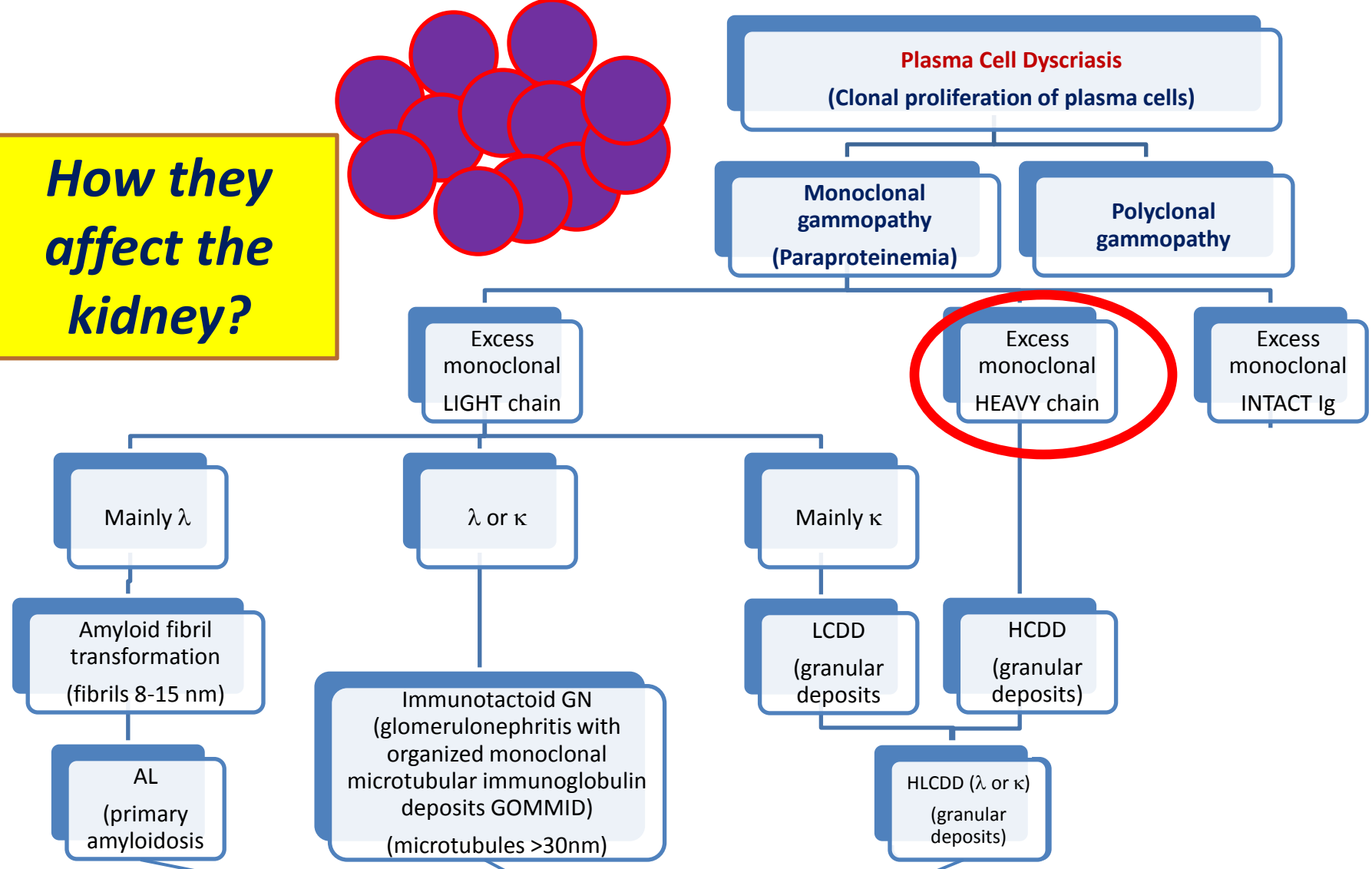
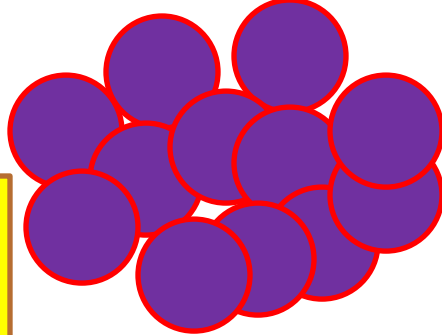
Copyright © 1998 by the National Kidney Foundation

*By electron microscopy, amyloid appears as randomly oriented thin fibrils, 10 to 12 nm in diameter, with a loose, flocculent background (transmission electron microscopy; original magnification x51,250).*

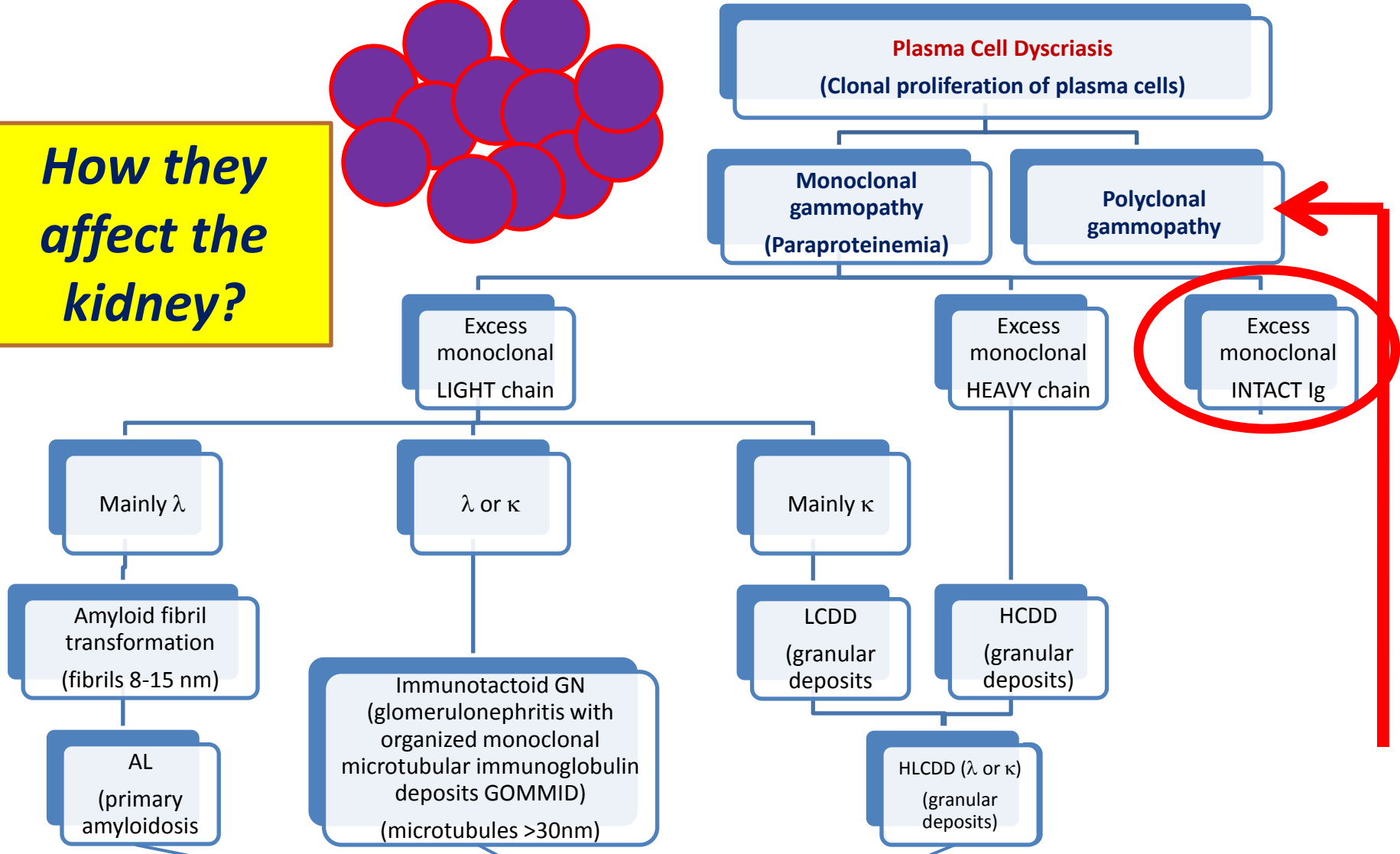
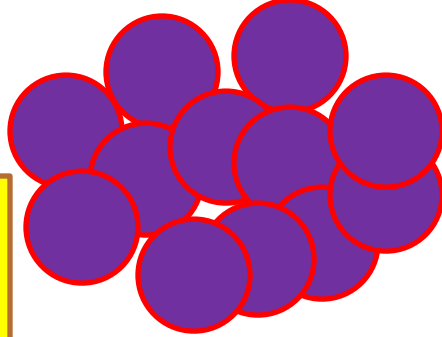
*How they  
affect the  
kidney?*



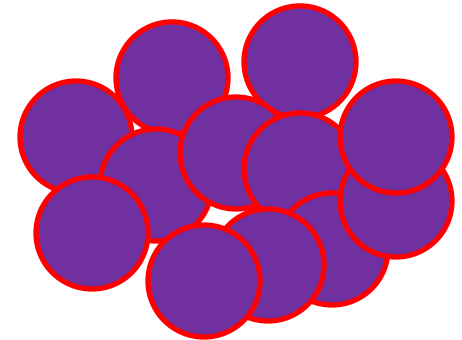
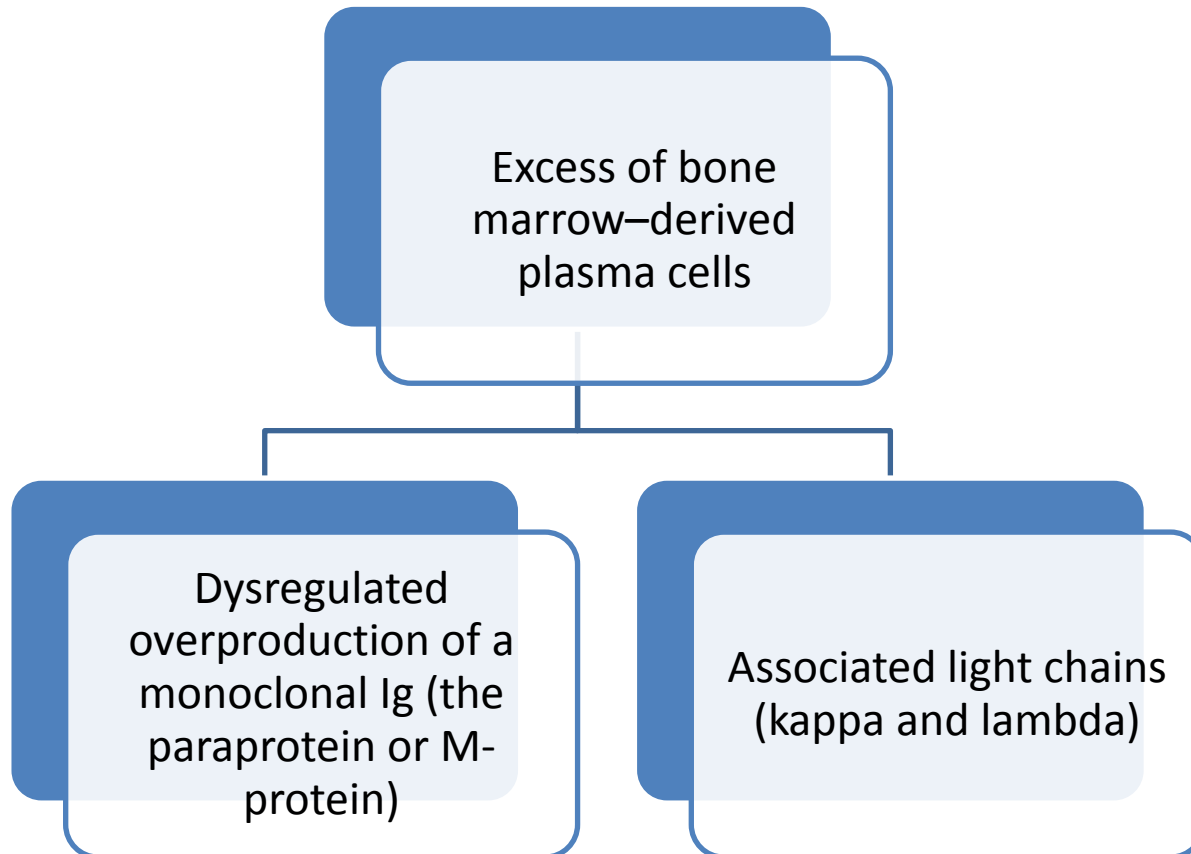
***How they  
affect the  
kidney?***



*How they  
affect the  
kidney?*



# What is Multiple Myeloma?



# When to suspect Multiple Myeloma?



**International  
Myeloma  
Foundation**

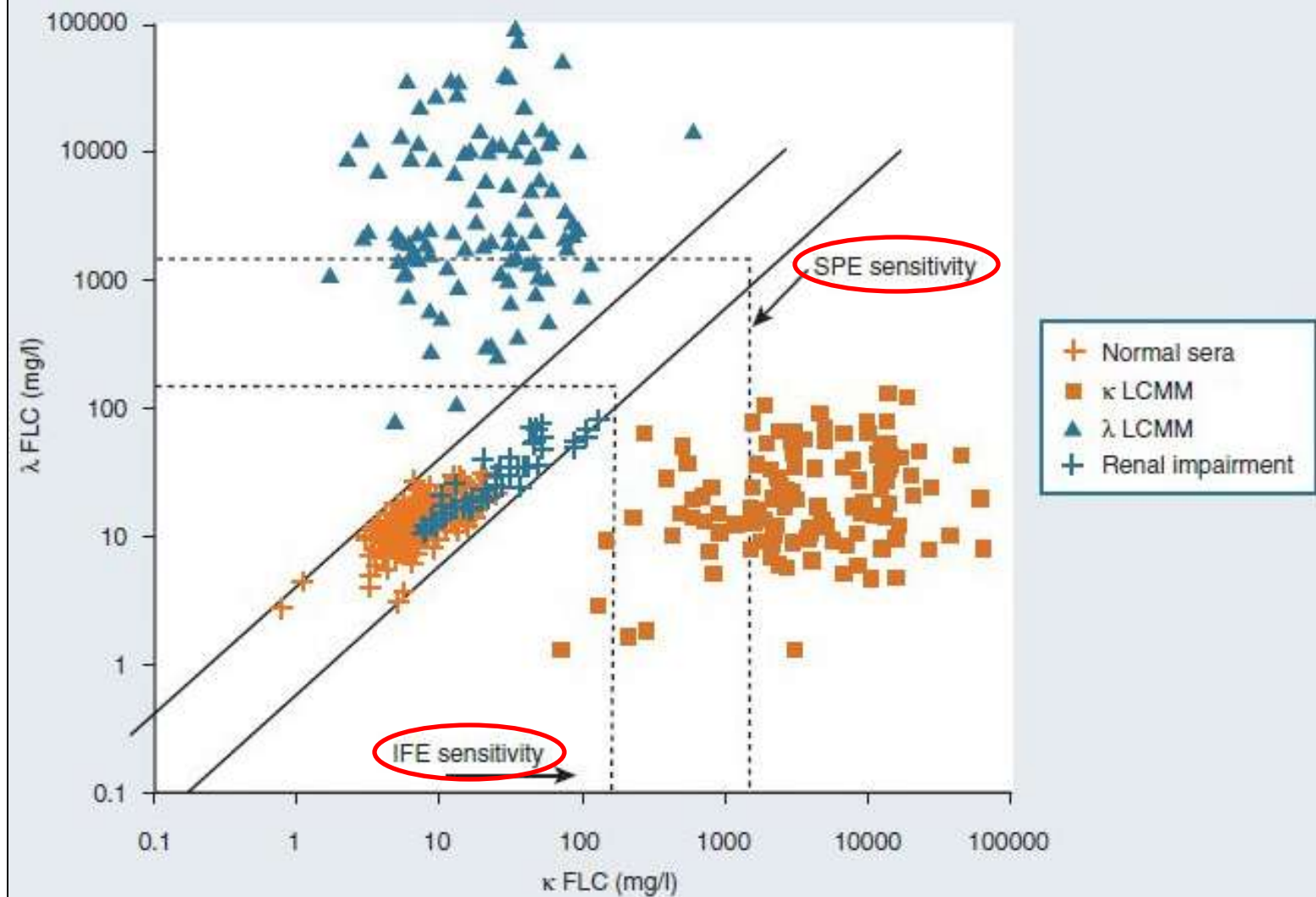
*Improving Lives • Finding the Cure®*

	MGUS	Smouldering (asymptomatic) myeloma	Active (symptomatic) myeloma
<b>Serum M-protein</b>	<3 g/100ml	≥3 g/100ml	≥3 g/100ml
<b>Bone marrow clonal plasma cells</b>	<10%	≥10%	≥10% or Plasmacytoma
<b>Related organ or tissue impairment</b>	Absent and No evidence of other B-cell proliferative disorders	Absent/ Asyptomatic	Requires 1 or more of the following: <ul style="list-style-type: none"> <li>• Calcium elevation</li> <li>• Renal insufficiency</li> <li>• Anaemia</li> <li>• Bone osteolytic lesion</li> </ul>

# Laboratory Diagnostic Tests

Serum protein electrophoresis (SPE)	Serum immunofixation electrophoresis (SIFE)
Can detect the whole immunoglobulin <i>(cannot reliably differentiate monoclonal from polyclonal light chain expansion)</i>	10 times more sensitive for immunoglobulins

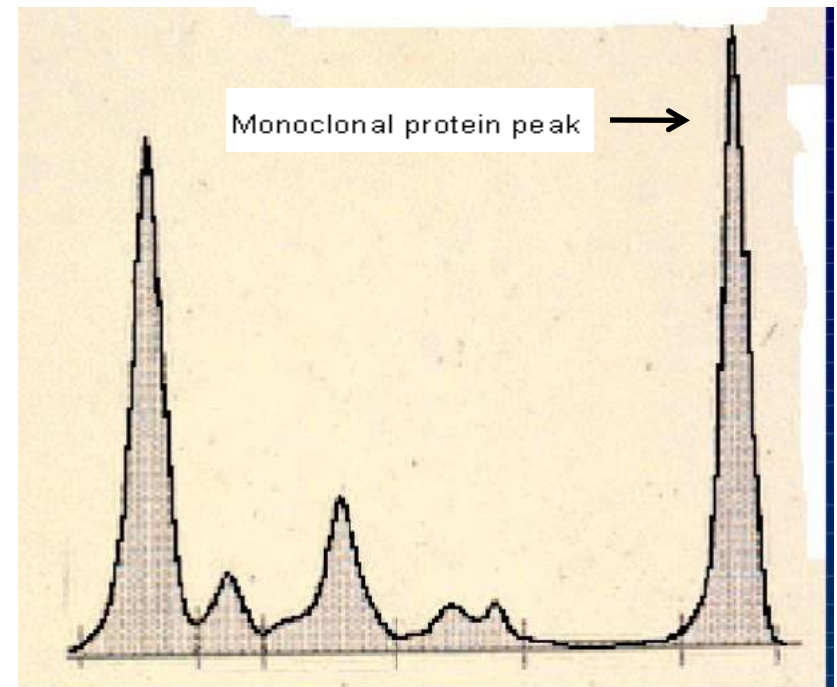
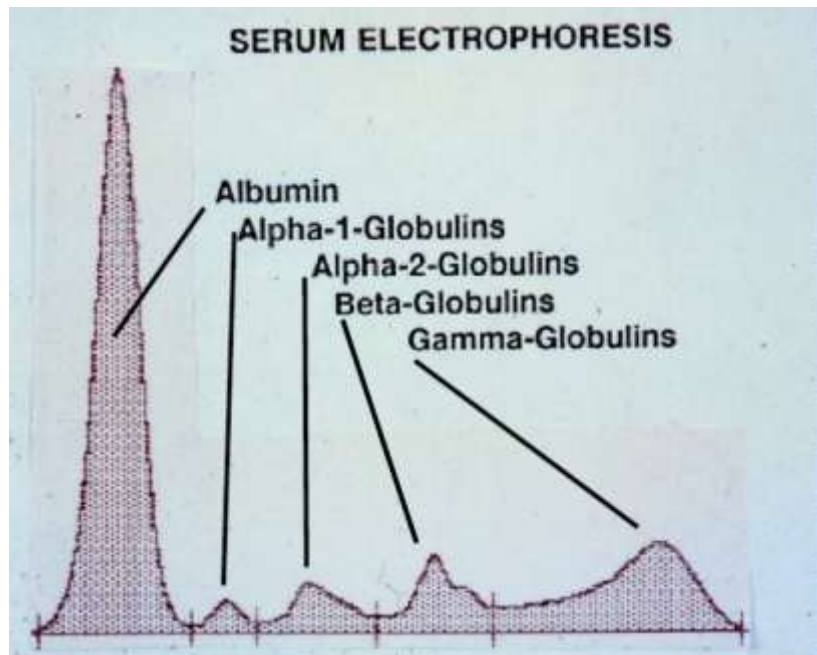
## Serum Free Light Chain Ratio and Values



# Serum protein electrophoresis (SPE)

## Paraprotein is

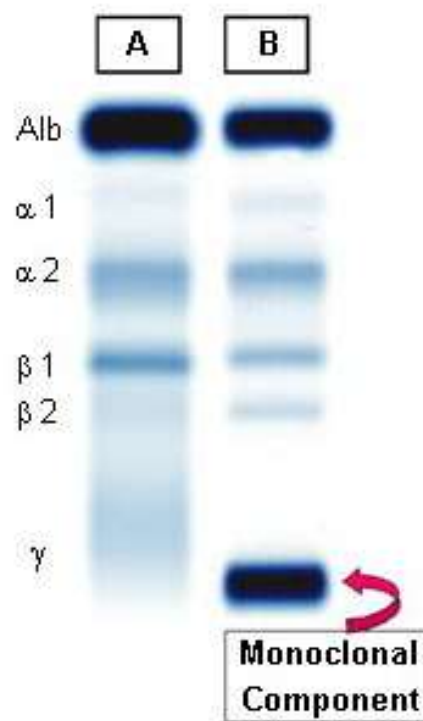
a monoclonal Ig (gamma globulin)  
that is produced in excess  
by the clonal proliferation of plasma cells.



# Serum protein electrophoresis (SPE)

## Paraprotein is

a monoclonal Ig (gamma globulin)  
that is produced in excess  
by the clonal proliferation of plasma cells.



# Laboratory Diagnostic Tests

Urine PEP, immunofixation  
electrophoresis (uIFS)  
*(to detect Bence Jones Proteinuria)*

Serum SPEP, immunofixation  
electrophoresis (sIFE)



**Dr. Henry Bence-Jones**  
31 December 1813 / / April 20, 1873

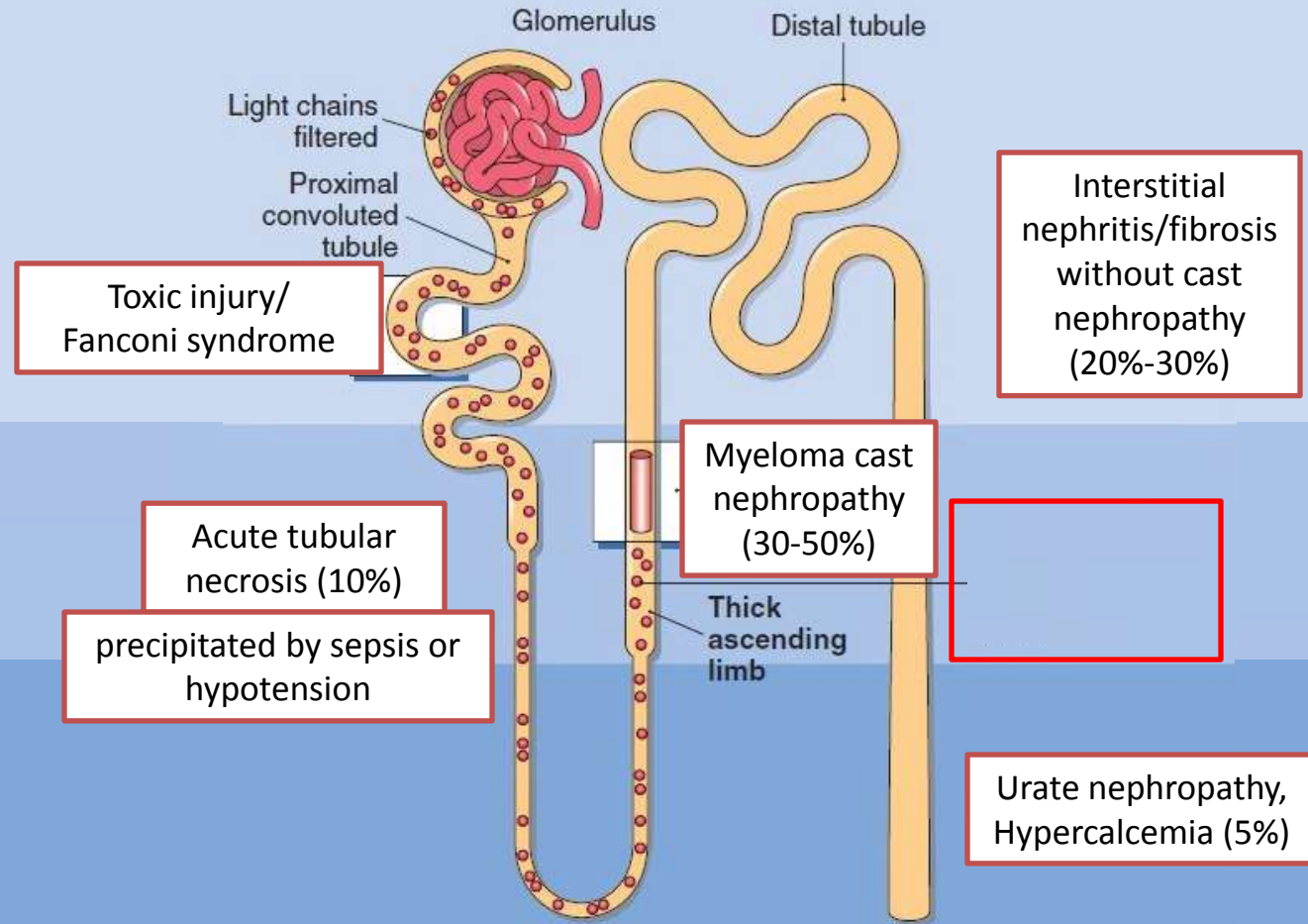
# Serum Free Light Chains ( $\kappa$ and $\lambda$ ) Measurement

This excess is detectable in the serum in MIDD, amyloid, or “nonsecretory” myeloma, in whom no monoclonal Ig has been identified with electrophoretic techniques.

Normal $\kappa/\lambda$	CKD $\kappa/\lambda$	Abnormal $\kappa/\lambda$ ratio
0.26–1.65		

This excess is detectable in the serum before urinary tubular catabolism is exceeded and before the SPE or IFE is abnormal

# How Multiple Myeloma affect the Kidney?



# Renal Pathology in Patients with Multiple Myeloma

Histological Finding	Prevalence
Myeloma kidney ( <i>Myeloma cast nephropathy</i> )	30%-50%
Interstitial nephritis/fibrosis without cast nephropathy	20%-30%
Amyloidosis	10%
Light chain deposition disease	5%
Acute tubular necrosis	10%
Other (urate nephropathy, tubular crystals, hypercalcemia, FSGS)	5%

	Myeloma Kidney	Other MIDDs
Proteinuria	<3 g/l	>3 g/l
Hematuria	Rare	LCDD, occasional Amyloidosis, rare
Hypercalcemia (or normal corrected calcium)	Common	Absent
Hypertension	Uncommon	LCDD common Amyloidosis uncommon
Cytopenias	Anemia very common Leukopenia and thrombocytopenia, occasional	Uncommon
Immunoparesis*	Very common	Uncommon
Lytic bone lesions	Very common	Absent
Renal impairment	Common	Common
Heavy chain	IgA, IgD, IgG	None
Type of light chain	Either	Amyloid $\lambda > \kappa$ LCDD $\kappa > \lambda$
Urinary light-chain excretion	Higher	Lower

# Clinical Tips & Tricks

## Diagnosis of Multiple Myeloma

### Urine Analysis

Patient with renal impairment  
and lower limb edema

Total protein quantification  
or specific urine  
electrophoresis &  
immunofixation.

Not detected by dipstick

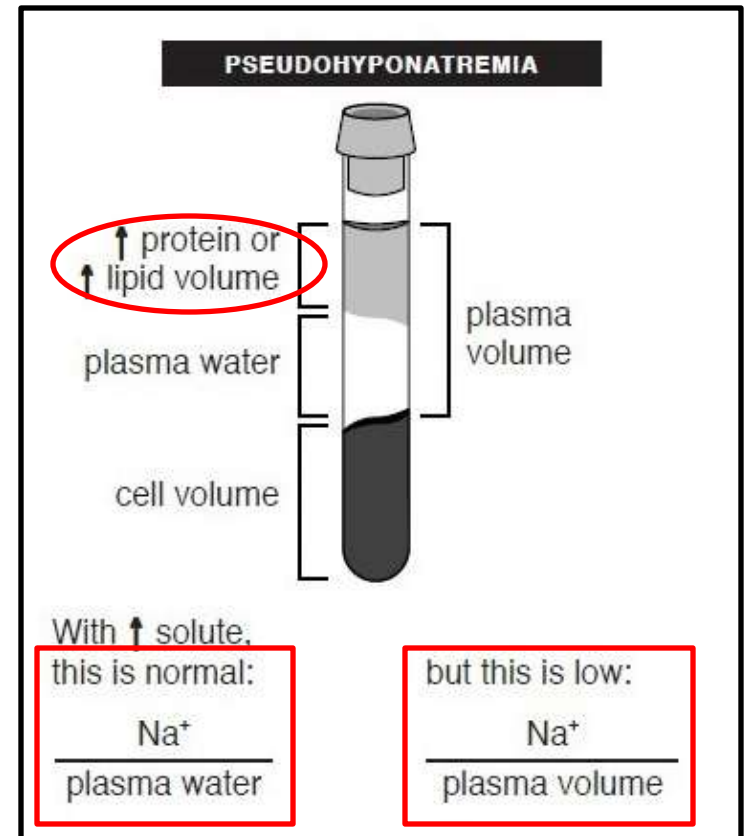
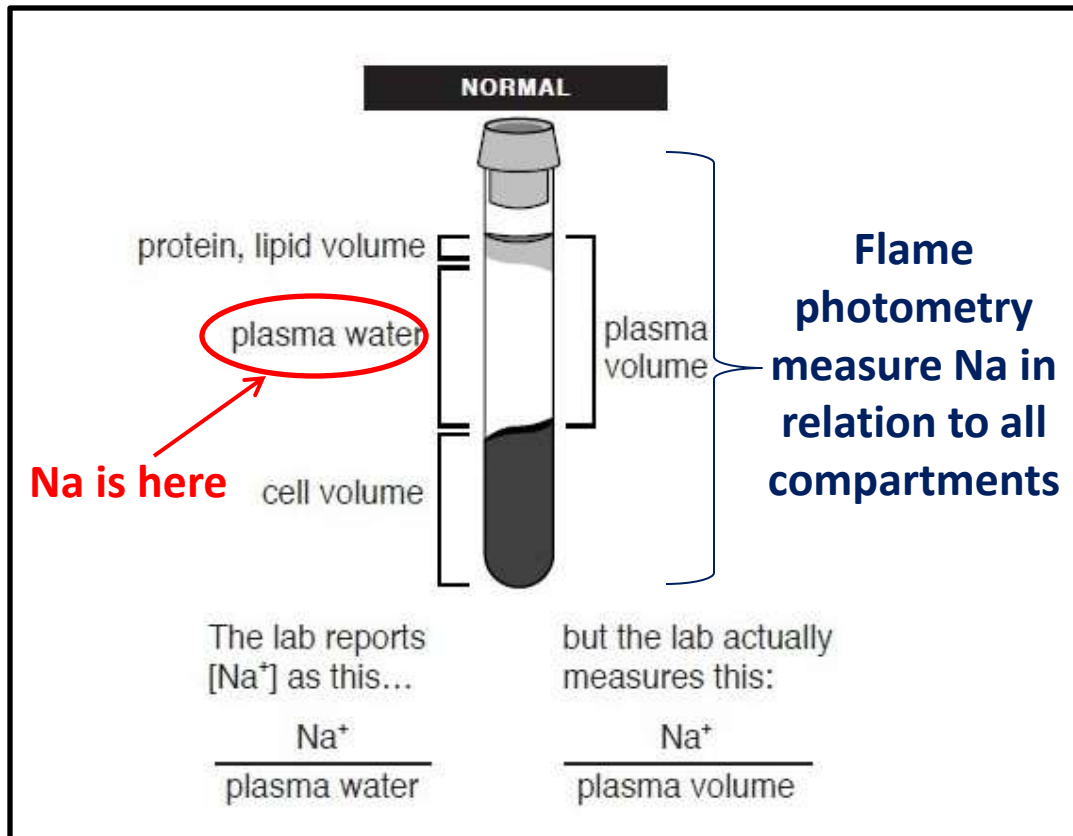
In Myeloma:  
increased urinary excretion  
of light chains



# Clinical Tips & Tricks

## Diagnosis of Multiple Myeloma

### Pseudo-Hyponatremia



# Clinical Tips & Tricks

## Diagnosis of Multiple Myeloma

### Pseudo-Hyponatremia

$$\text{Corrected Na} = \frac{\text{Serum Na} \times 93}{99 - 1.03 (\text{triglyceride gm/L}) - 0.73 (\text{protein gm/L})}$$

# Clinical Tips & Tricks

## Diagnosis of Multiple Myeloma

### Pseudo-Hyponatremia

Therefore, for patients with marked elevations in plasma lipids or plasma proteins, ask the hospital laboratory to use an ion-specific electrode to measure the plasma sodium concentration.

A diagnosis of a plasma cell dyscrasia is not always known prior to the discovery of abnormal kidney function.

The renal biopsy, performed to identify the responsible lesion, is not infrequently the initial indication of a plasma cell dyscrasia.

**[www.nephrotube.blogspot.com](http://www.nephrotube.blogspot.com)**

***facebook group: NephroTube***



Thank you!

Mohammed Abdel Gawad  
[drgawad@gmail.com](mailto:drgawad@gmail.com)